REMARKS

Reconsideration of the present Application in view of the present Amendments and the following remarks is respectfully requested. Claims 2, 7-14, and 51-59 are currently under examination in this Application. Applicants acknowledge and thank the Examiner for indicating that claims 2 and 7 are allowable. Applicants hereby cancel claims 11, 51-52, 54-59 without acquiescence to any rejection and without prejudice to further prosecution of this subject matter in a related divisional, continuation, or continuation-in-part application. Applicants have amended claims 8, 10, 12, 14, and 53 to particularly point out and distinctly claim the subject matter encompassed by Applicants' invention. Support for the amended claims may be found in the specification, for example, at page 7, lines 17-28; page 8, lines 3-15; and page 9, line 3 through page 10, line 2. No new matter has been added.

CLAIM OBJECTIONS

The PTO objects to claims 12 and 13 as being improper under 37 C.F.R. §1.75(c), asserting that the claims are multiple dependent claims that depend from multiple dependent claims.

Applicants respectfully submit that in view of the Amendments submitted herewith, the grounds for this objection have been obviated. Claim 12, upon which claim 13 depends, has been amended to recite dependency only on claim 10. Accordingly, Applicants respectfully submit that all claims are in proper form for allowance as required under 37 C.F.R. §1.75(c), and request that this objection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The PTO rejects claims 8-14 and 51-59 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The PTO concedes that the instant specification is enabling for a polynucleotide encoding SEQ ID NO:2, including SEQ ID NO:1 and degenerate variants thereof. The PTO alleges, however, that the specification does not enable a skilled artisan to make and use, without undue experimentation, a polynucleotide that encodes a polypeptide capable of dephosphorylating an activated MAP-kinase and that is at least 70%, 80%, or 90% identical to a

polynucleotide encoding an amino acid sequence set forth in SEQ ID NO:2, wherein the polypeptide comprises Asp73 and/or SEQ ID NO:3. The PTO further asserts that the scope of the claims is not commensurate with the disclosure in the specification.

Applicants respectfully traverse this rejection and submit that as disclosed in the present specification and recited in the instant claims, Applicants fully enabled the claimed invention at the time the Application was filed. Applicants submit that the specification provides explicit guidance enabling a person skilled in the art to make and use the claimed polynucleotides, including polynucleotide variants, readily and without undue experimentation. As taught in the present specification, the claimed polynucleotides encode a dual specificity phosphatase-2 (DSP-2) polypeptide that has the ability to dephosphorylate phosphorylated tyrosine and serine/threonine residues of a DSP-2 substrate (*e.g.*, at page 5, line 29 through page 6, line 4).

Contrary to the PTO's assertions, Applicants submit that the instant claims are commensurate in scope with the disclosure of the specification. The present specification teaches a skilled person how to make and use a polynucleotide variant that (i) encodes a polypeptide capable of dephosphorylating an activated MAP-kinase, (ii) comprises a sequence that encodes the peptide sequence SEQ ID NO:3, and (iii) is at least 90% identical to a polynucleotide that encodes a polypeptide comprising the sequence of SEQ ID NO:2 (*see, e.g.*, page 7, line 3 through page 8, line 2; page 9, line 3 through page 10, line 7; page 11, lines 12-20; page 15, line 27 through page 17, line 16).

The PTO concedes that determination of percent identity between two given sequences is possible. The PTO further concedes that "methods to produce variants of a known sequence are well known to the skilled artisan." The PTO asserts, however, that the present enablement rejection relates "to how to make a variant sequence that will be aligned." (*See* Action at page 7.) Applicants submit that if a skilled artisan desires to make a polynucleotide variant encoding a DSP-2 polypeptide, the skilled artisan would begin the process using the polynucleotide sequence and the encoded DSP-2 polypeptide sequence that are clearly disclosed in the specification, and then generate variants using methods that are also described in the specification and known in the art. Only an unskilled artisan, and *not* the obligatorily skilled

artisan, would expect to make a DSP-2 polypeptide-encoding variant polynucleotide, as the Action suggests, by randomly generating polynucleotides and then attempting to select a desired variant from the resulting complex milieu. Applicants are not required to enable an unskilled artisan (or a even skilled artisan) to make the claimed polynucleotides and their encoded products by using unsound scientific methods.

As clearly provided by the specification, whether an unknown polynucleotide shares 90% identity with a polynucleotide encoding a DSP-2 polypeptide can be readily determined by aligning the appropriate sequence disclosed in the present application with either the unknown polynucleotide sequence or the polypeptide sequence that it encodes, according to alignment methods described therein and known in the art (*see, e.g.,* page 9, lines 3-16). Methods for detecting phosphatase activity of a DSP-2 polypeptide are also taught in the specification based on catalytic assays known to the art (*see, e.g.,* page 25, lines 10-20). Applicants submit that in view of the abundant guidance and direction provided in the specification, the advanced state of the art, and the high level of skill of a person practicing the art, the specification enables a skilled artisan to make and use the claimed polynucleotide variants readily and without undue experimentation. (*See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

Applicants respectfully submit that, contrary to the assertion by the PTO, the specification teaches a person skilled in the art what are the structural and functional properties of a variant DSP-2 polypeptide encoded by the claimed polynucleotide variants. As taught in the present specification (*e.g.*, at page 5, line 29 through page 6, line 4) and recited in the instant claims, polynucleotides that encode a DSP-2 polypeptide, or a variant thereof, have the ability to dephosphorylate phosphorylated tyrosine and serine/threonine residues of a DSP-2 substrate (*functional property*). Methods for detecting DSP-2 catalytic activity are taught in the specification (*see, e.g.,* page 25, lines 10-20).

The specification further describes as a *structural* feature the conserved dual specificity phosphatase signature active site motif, C-X_5-R, which is present in the peptide LHCAAGVSRS (SEQ ID NO:3) (active site motif underlined) within the DSP-2 polypeptide sequence encoded by the claimed polynucleotides (*see, e.g.,* page 11, lines 12-20; page 30, lines

7-12, and references cited therein; SEQ ID NO:1 and SEQ ID NO:2; *see also, e.g.*, Keyse, *Biochim. Biophys. Acta* 1265:152-60 (1995)). For example, and as described in the specification, substitution of the cysteine residue within this active site motif results in a loss of phosphatase activity (*see, e.g.,* page 6, line 13 through page 7, line 2, and references cited therein). The specification also teaches that when an invariant aspartic acid residue at position 73 in SEQ ID NO:2 is substituted with another amino acid, the resulting polypeptide, called a substrate trapping mutant, has a reduced ability to dephosphorylate a substrate (*see id.*). Thus, the specification has identified a region (SEQ ID NO:3) and positions within the DSP-2 polypeptide (an invariant aspartate residue and a cysteine residue within the active site motif) that are not amenable to modification, and if mutations are introduced at these positions, the resulting polypeptide has a reduced ability to dephosphorylate an activated MAP-kinase. Whether a "fragment corresponding to SEQ ID NO:3 is unlikely to exhibit DSP-2 activity," as asserted by the PTO, is irrelevant; the DSP-2 polypeptide that is encoded by the claimed polynucleotide contains SEQ ID NO:3 and exhibits phosphatase catalytic activity, and the claimed polynucleotide comprises a sequence at least 90% identical to a polynucleotide that encodes a polypeptide comprising SEQ ID NO:2.

Given the disclosure in the specification of a polynucleotide (*e.g.,* SEQ ID NO:1) encoding a DSP-2 polypeptide (SEQ ID NO:2) and methods taught in the specification and known in the art for making and identifying DSP-2 variants with phosphatase activity (*e.g.,* page 8, line 25 through page 10, line 2; page 11, lines 12-29; page 25, lines 10-20), a skilled artisan is therefore enabled by the instant disclosure to make and use the claimed polynucleotide variants readily and without undue experimentation. The specification clearly describes DSP-2 amino acid residues and DSP-2 polypeptide regions, which, if changed, result in compromised phosphatase activity (*see, e.g.,* page 6, line 13 through page 7, line 2). That is, the specification describes the location and identity in a DSP-2 polypeptide of amino acids that contribute to DSP-2 catalytic dephosphorylation activity, and which therefore are not amenable to modification in the design of a functional (*i.e.,* catalytically active) DSP-2 variant. Given such description in the specification, the person skilled in the art may reasonably and rationally predict that modifications not affecting catalytic activity may be made to residues that are not implicated in

catalytic activity. According to textbook knowledge in the molecular biology arts with respect to enzymes, "[in] fact, evidence now indicates that amino acid replacements in many parts of a polypeptide chain can occur without seriously modifying catalytic activity" *(see Molecular Biology of the Gene*, page 227 (James D. Watson et al., ed., The Benjamin/Cummings Publishing Co., (Menlo Park, CA) (4th ed. 1987)). Particularly, as taught in the specification and understood in the art, a skilled artisan would expect that the secondary structure and hydropathic nature of the DSP-2 polypeptide would be substantially unchanged if a conservative amino acid substitution were made to such residues, that is, conservative modifications would be tolerated (*see, e.g.,* specification at page 7, lines 3-16).

Applicants also respectfully disagree with the assertion by the PTO that screening for multiple modifications is not routine. Random mutagenesis techniques, such as alanine scanning mutagenesis, error prone polymerase chain reaction mutagenesis, and oligonucleotide-directed mutagenesis, some of which generate tens of thousands of mutants, are well known and have been used extensively in the art (*see, e.g.,* Sambrook et al. *Molecular Cloning: A Laboratory Manual*, 3rd ed., Cold Spring Harbor Laboratory Press, NY (2001)). Even assuming *arguendo*, as the PTO asserts, that it cannot be predicted which positions within a protein's sequence can tolerate a substitution, deletion, or insertion of an amino acid, persons skilled in the art can alleviate these difficulties by developing independent assays for assessing folding of the protein of interest (*see, e.g.,* Sambrook et al., page 13.3). Such assays commonly include, for example, the ability of the protein to react with mono- or polyclonal antibodies that are specific for native or unfolded epitopes, the retention of catalytic or ligand-binding functions, the sensitivity or resistance of the mutant protein to digestion with proteases, and other functional assays that characterize a particular polypeptide (*see* Sambrook et al., page 13.3; *see also, e.g.,* specification at page 17, line 19 through page 19, line 7; page 19, line 10 through page 21, line 9; page 25, line 10 through page 26, line 10). Sambrook et al. further teach that the functions of proteins can be mapped to specific structural domains and that by genetic engineering of the protein, undesirable activities of enzymes can be eliminated while their desirable catalytic and/or physical properties can be enhanced. "In short, oligonucleotide-mutagenesis has become the genetic engineer's alchemy." (Sambrook et al., page 13.4).

While identifying DSP-2 variants generated by any of the commonly used mutagenesis techniques may involve screening a large number of molecules, such experimentation is not undue. To determine the phosphatase activity of a DSP-2 variant, a skilled artisan, using methods provided in the specification and known in the art, can readily analyze dephosphorylation of a DSP-2 substrate (*see, e.g.,* page 15, line 26 through page 17, line 16; page 25, line 10 through page 26, line 10). Given the teachings of the present specification and, *inter alia*, the level of skill in the art, performing such assays to determine whether an encoded polypeptide has DSP-2 phosphatase activity would not amount to undue experimentation, but instead is merely a matter of permissible routine screening. (*See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (The test for enablement is not merely quantitative "since a considerable amount of experimentation is permissible.")).

As discussed in detail herein, the instant claims encompass a finite number of highly related polynucleotides, and the specification provides ample guidance for a skilled artisan to make and use the claimed polynucleotides and their encoded products readily and without undue experimentation. Furthermore, it is well settled that to satisfy the enablement requirement, an Applicant need not test every embodiment of an invention encompassed by a claim and need not describe a large number of examples, particularly when (as here) the level of skill in the art is high and the teachings of the specification are ample. *See In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (C.C.P.A. 1982) (finding that although the invention encompassed a large variety of compounds, a large number of examples would not be required because examples are not required to satisfy section 112, first paragraph). Moreover, even though a large number of polynucleotide variants may be made, Applicants are not required to list all operable embodiments of the invention and to exclude inoperable ones, if any. *See Atlas Powder Co. v. E. I. Dupont de Nemours & Co.,* 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Accordingly, Applicants submit that given the disclosure of the present Application, the state of the art, and the level of skill in the art, the specification enables a skilled artisan to make and use the claimed polynucleotides, readily and without undue experimentation. Applicants therefore respectfully submit that the Application satisfies all requirements under 35 U.S.C. § 112, first paragraph, and request that the rejection of the claims be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The PTO rejects claims 8-14 and 54-56 under 35 U.S.C. 112, second paragraph, for indefiniteness. Specifically, with respect to claim 11, the PTO alleges that a polynucleotide that hybridizes to SEQ ID NO:1 under the recited conditions and that exhibits at least 70% identity to SEQ ID NO:1 renders the scope of the claimed polynucleotide unascertainable. The PTO asserts that a polynucleotide that hybridizes to SEQ ID NO:1 under the conditions recited will have greater than 70% nucleotide identity to SEQ ID NO:1.

The PTO alleges that claims 54-56 are confusing and not clearly directed to a polynucleotide encoding SEQ ID NO:2 or to a polynucleotide encoding a variant of SEQ ID NO:2. The PTO asserts that if the claims are intended to be directed to a polynucleotide that encodes a polypeptide having an amino acid sequence set forth in SEQ ID NO:2, the recitations that the polypeptide comprises aspartic acid at position 73 and comprises the amino sequence set forth in SEQ ID NO:3 are redundant.

The PTO also alleges that claim 14 is unclear. In particular, the PTO asserts that the claim is directed to a method of producing a DSP-2 polypeptide but that claims 51-56, from which claim 14 depends, instead "recite a polypeptide capable of dephosphorylating an activated mitogen-activated protein kinase (MAP-kinase)."

Applicants respectfully traverse these rejections and submit that the instant claims particularly point out and distinctly claim what Applicants regard as their invention. Applicants submit that the rejection of claims 54-56 is rendered moot in view of the Amendments submitted herewith, which include cancellation of claims 54-56.

Applicants submit that the metes and bounds of the instant claims, when read in light of the specification, are readily ascertainable. Regarding claim 11, the meanings of the recited features pertaining to hyribidization conditions, percent sequence identity, catalytic activity, and the structure of SEQ ID NO:3 are unambiguously clear (*see, e.g.,* specification at page 5, line 29 through page 6, line 4; page 9, line 3 through page 10, line 2; page 11, lines 12-20; page 15, line 27 through page 17, line 16). Contrary to the assertion in the Action, a polynucleotide that exhibits at least 70% nucleotide identity to SEQ ID NO:1, for example, a

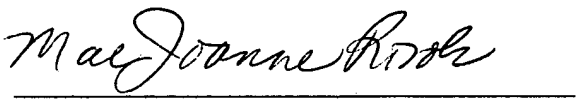
polynucleotide that does not contain the 5' and 3' non-coding portions of SEQ ID NO:1, would hybridize to SEQ ID NO:1 according to established principles of nucleotide base complementarity (*see, e.g.,* specification, page 9, line 3 through page 10, line 2; Figure 1). Nevertheless, without acquiescence to any rejection and solely for purposes of advancing prosecution, claim 11 is cancelled herewith without prejudice, rendering moot the outstanding rejection.

With respect to claim 14, Applicants respectfully traverse the rejection and submit that the meaning of what is encompassed by the claim is clear. Claim 14 particularly points out and distinctly claims a method for producing a polypeptide that either (i) comprises the amino acid sequence set forth in SEQ ID NO:2 or (ii) is capable of dephosphorylating an activated MAP kinase and is encoded by a polynucleotide having a sequence at least 90% identical to a polynucleotide that encodes SEQ ID NO:2 (*see, e.g.,* specification at page 8, lines 3-15). Accordingly, Applicants submit that no ambiguity exists with respect to what are the metes and bounds of the claimed subject matter, and in particular, what is the product of the recited method.

In view of the present Amendments and the above remarks, Applicants respectfully submit that the instant claims meet the requirements for definiteness under 35 U.S.C. § 112, second paragraph. Applicants therefore request that the rejection of these claims be withdrawn.

Applicants respectfully submit that all claims remaining in the Application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,
SEED Intellectual Property Law Group PLLC



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